REMARKS

Reconsideration of this Application is respectfully requested.

Receipt of the Office action mailed on January 17, 2003 is acknowledged. Upon entry of the foregoing amendments, claims 1-6, 8-12 and 14-18 are pending in the application, with claim 1 being the only independent claim. Claims 7 and 13 are hereby cancelled without prejudice. Claims 16-18 have been newly added and support for said claims can be found in Examples 6-8 and page 17, lines 4-17.

In the Non-final Office action mailed on January 17, 2003, the Examiner set forth a number of grounds for rejection of the claims. These grounds are addressed individually and in detail below.

Double Patenting

Claims 1-7 and 13-15 were provisionally rejected under the doctrine of obviousness type double patenting as being unpatentable over claims 1-4 and 9 of co-pending application 09/070,938 (hereinafter "the '938 application"). At the outset, the claims as presently pending in the '938 application are directed to an RNA complex, a packaging cell, and methods for making same. No claims are directed to methods of using such materials for transferring nucleic acids into nerve cells, as particularly claimed herein in claims 1-5, 8-12 and 14-18. Products and methods of using them comprise distinct categories of invention and claims to one cannot render obvious claims to the other unless they comprise elements that restrict them to a singular use or singular product. Such is not the case here. Thus, contrary to the Examiner's assertion, the conflicting claims are indeed patentably distinct. Moreover, with respect to the claims presently at issue, a grant of rights to one set of claims would not result in an extension of

monopoly with respect to the other set, and vice versa. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 1-7 and 13-15 were also provisionally rejected under the doctrine of obvious type double patenting for being unpatentable over claims 1-16 of co-pending application 09/762,641 (hereinafter "the '641 application"). As the Examiner noted, the claims of the '641 application are drawn to a method of using the RNA construct. The instantly claimed method is a species of the method claimed in the '641 application. Therefore, Applicants will submit a terminal disclaimer when the claimed invention is noted to otherwise be allowable.

Specification

The Examiner objected to the specification based upon certain alleged informalities. Specifically, the Examiner objected to the phrase "38°C to 38°C" on page 18, line 29 and page 19, line 25 as being an imprecise temperature and the phrase "brain region containing were made into" on page 19, line 29 as grammatically incorrect. The Applicant has amended the specification to correct these informalities.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description Requirement

The Examiner alleges that the claims are drawn to a broad genus of viruses, a negative sense RNA viral vector, and that the genus claims encompass a wide array of virus. The Examiner further alleges that the specification discloses only one example of such a virus (namely, Sendai virus), that the Applicant fails to disclose what genes or components of Sendai virus are required to function as a viral vector for the transfer of

genetic material to nerve cells, and that the Applicant does not disclose any of the variants or modifications embraced by such a broad genus of viral vectors.

In response, Applicants have amended negative-sense RNA virus to that belonging to the Paramyxoviridae family as shown in the amended claims. The specification discloses the structure of Sendai virus containing six genes, NP, P/C, L, M, F, and HN genes (page 4, lines 3-19). This structure is common in other paramyxoviruses as illustrated in Conzelmann K. K. Annu. Rev. Genet. 32:123-62, 1998 (Appendix A); this literature discloses other structural and functional similarities for paramyxoviruses. Therefore, one skilled in the art would have readily expected that paramyxoviruses other than Sendai virus can be used in the instant invention. Accordingly, in view of the knowledge in the art, the exemplary description of Sendai virus set forth in the specification is sufficient to indicate that the Applicants had possession of the presently claimed invention so as to satisfy the written description requirement.

The Examiner further alleges that Applicants have not adequately described the broad genus of "secretory proteins," sufficient to demonstrate "possession of all secretory proteins embraced by the breadth of the claims." In response, Applicants have cancelled claim 7. Instead, Applicants add claim 18 reciting a protein regulating food intake, which is supported by Example 9.

Enablement

Claims 1-10 and 13-15 were rejected under 35 U.S.C. §112, first paragraph on the assertion that the specification, while being enabling for *in vivo* methods for gene therapy in rats and mice, does not reasonably provide enablement for *in vivo* methods in other

organisms. To support this rejection, the Examiner cites to the significant hurdles in the art of *in vivo* foreign gene delivery and expression, particularly as to efficiency of gene transfer and expression (see Anderson, et al.) as well as the inherent difficulties in targeting intended cells and achieving long term expression of the transgene (see Verma, et al. and Palu, et al.) and the unpredictability of gene therapy extrapolated to human systems (see Crystal, et al.)

Applicants have now restricted claim 1 to Paramyxovirus and local administration. In view of these amendments, the claimed invention is sufficiently described in the specification so as to enable one skilled in the art to practice *in vivo* methods for gene therapy in organisms other than rats and mice.

The "evidence" cited by the Examiner is not pertinent to the claimed invention. Specifically, the art fails to challenge the utility and operability of negative strand DNA viral vectors, particularly those derived from Paramyxoviruses such as Sendai virus. For example, the cited prior art, most particularly Verma, et al. and Anderson, et al., discuss drawbacks associated with viral vectors derived from retroviruses, lentiviruses, and adenoviruses, as well as other viruses such as HSV, HIV, HTLV, MuLV, Sindbis virus, semliki forest virus, and vaccinia virus. However, none of these are negative strand RNA viruses, much less Paramyxoviruses. Negative strand RNA viruses have advantages, such as "protein expression in short time after invention and an extremely higher level expression of the transgene product compared with adenovirus" (see specification, page 2, lines 4-7). Thus, prior art discussing the hurdles associated with adenoviral vectors and the like is not dispositive on the issue on the enablement of Paramyxoviral vectors. The generic doubts of the prior art are assuaged by the concrete proof of principle

experiments set forth in Applicants specification. See particularly Examples 8, 9, and 10, which conclusively demonstrate the ability of the Sendai viral vectors to locally deliver a desired foreign gene to a target cell population.

Palu, et al. discuss the need to specifically tailor the delivery system to the individual disease. This is exactly what Applicants have done. They have demonstrated that the specifically claimed vector (i.e., Paramyxoviral vectors) can deliver nucleic acids to specific cells (i.e., nerve cells such as ependymal cells and pyramidal cells of the hippocampus) *in vivo* with the requisite level of efficiency necessary to ensure therapeutic results (again, see Example 8-10).

Finally, while Verma, et al. note that the inability to deliver genes efficiently and to obtain sustained expression are indeed major problems, they conclude that these problems are surmountable and that in the not too distant future, gene therapy will become as routine a practice as heart transplants are today. Thus, gene therapy is not *per se* a suspect science.

The Examiner cites Crystal, et al. and Gura, et al. to support the premise that gene therapy cannot be extrapolated from animal models to human systems. However, Applicants believe the Examiner has taken the prior art out of context. In the opening abstract, Crystal, et al. expressly state that "enough information has been gained from clinical trials to allow the conclusion that human gene transfer is feasible, can evoke biologic responses that are relevant to human diseases" and that "adverse events have been uncommon and have been related to the gene delivery strategies (i.e., the delivery system);" while "human gene transfer still faces significant hurdles before it becomes an established therapeutic strategy," "its accomplishments to date are impressive and the

logic of the potential usefulness of the clinical paradigm continues to be compelling." Furthermore, Applicants submit that the Examiner is holding Applicants to a higher standard than is required by 35 U.S.C. §112, first paragraph. The standard is not absolute predictability but objective enablement – would one of ordinary skill in the art be able to make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation? Evidence provided by Applicants need not be conclusive but merely convincing to one of ordinary skill in the art (see MPEP §2164.05). In this case, Applicants submit that the compelling animal data is sufficiently "convincing" that one of ordinary skill in the art would not doubt its feasibility or its application to mammals other than rodents.

Moreover, if we were to follow the Examiner's rule, Applicants would have to submit conclusive data from human clinical trials before they would be granted rights to an *in vivo* gene therapy applicable to humans. This is clearly in conflict with the statute, the rules and the guidelines of the MPEP. Therefore, Applicants respectfully request that the rejections be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-10 and 13-15 were rejected under 35 U.S.C. §112, second paragraph, for being vague and indefinite on the assertion that it is unclear whether claim one is drawn to a method or inappropriately to a method and a product. To remove any possible ambiguity, claim 1 has been amended to recite, "a step of contacting the nerve cells with either (a) a negative-sense RNA viral vector or (b) cells comprising said vector." Therefore, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all currently outstanding objections and rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, that the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Response is respectfully requested.

Respectfully submitted,

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